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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Lee et al	§	**ART UNIT: 1647**
	§	
FILED: November 16, 2000	§	**EXAMINER:**
	§	**Bunner, B.**
SERIAL NO.: 09/714,692	§	
	§	
FOR: Method of Inhibiting Angiogenesis	§	
By Administration of A Corticotropin	§	**DOCKET:**
Releasing Factor Receptor 2 Agonist	§	**D6233CIP**

Mail Stop AF
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313

TRANSMITTAL OF APPEAL BRIEF AND CERTIFICATE OF MAILING UNDER 37 CFR 1.8

Dear Sir:

Enclosed please find three originals of the Appeal Brief for the above-referenced patent application.

The Commissioner is hereby authorized to charge Deposit Account No. 07-1185 in the total amount of $160 for the appeal fee and any additional fee that may be required. Please credit any overpayment or debit any underpayment to Deposit Account 07-1185.

I hereby certify under 37 CFR 1.8 that the following correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to Mail Stop AF, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313. Please return the enclosed postcard acknowledging receipt of this correspondence.

Respectfully submitted,

Date: July 23, 2003

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ATTENTION: Board of Patent Appeals and Interferences

APPELLANT'S BRIEF

This Brief is in furtherance of the Notice of Appeal filed in this case on June 11, 2003. The fees required under 37 C.F.R. §1.17(f) and any other required fees are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

In accordance with 37 C.F.R. §1.192(a), this Brief is submitted in triplicate.

INDEX OF SUBJECT MATTER

I. REAL PARTY IN INTEREST

The real party in interest is Research Development Foundation, the Assignee, as evidenced by an Assignment recorded in the Patent and Trademark Office at Reel 011466, Frame 0830 on January 26, 2001.

II. RELATED APPEALS AND INTERFERENCES

Appellant is aware of no other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF THE CLAIMS

Originally claims 1-27 were filed with this Application. Claims 1-19 and 24-27 were withdrawn from consideration. The pending claims 20-23 are being appealed of which claim 20 is an independent claim.

IV. STATUS OF AMENDMENTS

No claim amendment was made subsequent to the final rejection mailed December 16, 2002. Pending claims 20-23 are shown in Appendix A.

V. SUMMARY OF THE INVENTION

The present invention provides data that indicate Corticotropin Releasing Factor Receptor 2 (CRFR2) null mutant mice exhibit an increase in the size and number of blood vessels in various tissues. Figure 7 shows an increase in number and size of blood vessels in the anterior pituitary (Figure 7B), white adipose tissue (Figure 7D) and dorsal brain surface (Figure 7F) in CRFR2 null mutant mice. Microfil perfused tissues also indicate increased vessel size and number in dorsal brain surface (Figure 9A), large intestine (Figure 9B) and heart (Figure 9C). The major vessels in kidney, adrenal glands and testis are significantly increased in size in CRFR2 null mutant mice relative to those of control mice (Figure

10). Since CRFR2 receptor and its activity have been localized within the endothelial cell layer of blood vessels, the data presented herein indicate that CRFR2 plays a significant role in regulating angiogenesis (page 48, lines 20-21; page 49, line 4). In view of the data disclosed herein, one of ordinary skill in the art would conclude that well-known CRFR2 agonists such as urocortin and CRF could be used to inhibit angiogenesis.

Claims 20-23 are directed to a method of using a CRFR2 agonist such as urocortin or CRF to inhibit angiogenesis in a target tissue such as heart, brain, pituitary, gonad, kidney, adipose, or the gastrointestinal tract. The method is applicable to an individual having cancer or diabetic retinopathy.

VI. ISSUES

35 U.S.C. §112

Whether claims 20-23 are enabled under 35 U.S.C. §112, first paragraph.

VII. GROUPING OF CLAIMS

The rejected claims do stand or fall together.

VIII. ARGUMENTS

The Rejection Under 35 U.S.C. §112

In the Final Office Action mailed December 16, 2002, claims 20-23 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. Applicants respectfully traverse this rejection.

Claims 20-23 are directed to a method of using a Corticotropin Releasing Factor Receptor 2 (CRFR2) agonist such as urocortin or corticotropin releasing factor to inhibit angiogenesis in a target tissue such as heart, brain, pituitary, gonad, kidney, adipose, or the gastrointestinal tract. The method is applicable to an individual having cancer or diabetic retinopathy.

The Examiner contends that the specification only outlines a prophetic procedure to inhibit angiogenesis in a target tissue by administering a CRFR2 agonist. The Examiner concludes that this does not provide sufficient guidance to the artist to use the current invention, but only an invitation to use the invention as a starting point for further experimentation. The Examiner argues that relevant literature reports that anti-angiogenic therapies have

been active in animal models but disappointing in clinical studies (Griffioen and Molema, 2000), and that the state of the art is such that delivering proteins and peptides non-invasively is problematic and unpredictable (Pettit and Gombotz, 1998; Simons et al., 2000). The Examiner concludes that the specification lacks working examples and other direction or guidance to enable one skilled in the art to practice the claimed invention without undue experimentation; therefore, claims 20-23 are not enabled according to the analysis of the *In re Wands* factors. Applicants respectfully disagree

The eight-factor *In re Wands* test for undue experimentation requires that a conclusion of nonenablement be based on the evidence as a whole (M.P.E.P. §2164.01(a)). It is improper to conclude that a disclosure is not enabling based on an analysis of only one factor while ignoring one or more of the other factors in the Wands test (M.P.E.P. §2164.01(a)). Besides the existence of a working example and the amount of guidance provided, other relevant factors include the state of the prior art, the level of one of ordinary skill, and the level of predictability in the art. Applicants respectfully submit that in view of the state of the art and the knowledge of one skilled in the art at the time of

filing, the present specification has provided sufficient disclosure to enable one so skilled to practice the claimed invention without undue experimentation.

With regard to the state of the art, it was known at the time of filing of the present application that pathological conditions such as tumor growth and diabetic retinopathy are characterized by abundant angiogenesis (Griffioen and Molema, page 239, column 2, first full paragraph). Griffioen outlines several molecular factors that are known to have key roles in the induction of angiogenesis, including the upregulation of vascular endothelial growth factor (VEGF). Vascular endothelial growth factor is suggested to be a major player in initiating angiogenesis because it induces vasodilation in response to nitric oxide production and increases endothelial cell permeability. Also, the vascular endothelial growth factor receptor is expressed under hypoxic or ischemic conditions, and is produced abundantly by hypoxic tumor cells (Griffioen, paragraph spanning pages 239-240). Griffioen suggests that one method to interfere with angiogenesis is to inhibit the action of angiogenesis-promoting factors, such as vascular endothelial growth factor (Griffioen, page 249, first column, first full paragraph).

Angiogenesis is also known to have an important role in chronic inflammation (Griffioen, Section IV.B, page 257-259). Vascular changes occur in the beginning stages of inflammation, including dilatation, increases in permeability, and endothelial cell activation. Many chronic inflammatory diseases in humans are characterized by angiogenesis, including rheumatoid arthritis. The blood vessels contribute to inflammation by producing cytokines, chemokines, and proteases. The inflamed rheumatoid synovium has tumor-like qualities, in that it invades and destroys its local environment and produces abnormal levels of angiogenesis-promoting cytokines, including vascular endothelial growth factor. Increased serum levels of vascular endothelial growth factor correlate with chronic inflammatory disease in patients; vascular endothelial growth factor may act through increasing vascular permeability and/or wound healing via its proangiogenic effects. Neovascularization has also been associated with diseases of the eye such as diabetic retinopathy, where elevation of vascular endothelial growth factor, E-selecting and ICAM-1 indicate a strong inflammatory component in such diseases.

Inflammation is also known to be involved in the process of tumor growth (Griffioen, page 259, first column, first full

paragraph). Inflammatory cells are present in the stromal area of various tumor types, which may account for cytokine production that attract additional inflammatory cells, and may have proangiogenic activity. Inflammation is followed by angiogenesis in wound healing. These observations have led to the idea that angiogenesis and inflammation exist at the same time, which in turn led to the idea that antiangiogenic therapies for the inhibition of tumor growth could be applied to the treatment of chronic inflammatory diseases as well (Griffioen, page 259, first column, second full paragraph; page 262, second column, first full paragraph).

The Griffioen reference indicates that it is well known in the art that angiogenesis plays an important role in a number of pathological conditions and inhibition of angiogenesis is expected to have beneficial effects in the treatment of cancer, chronic inflammation and other diseases. In view of this background in the art, the present application further demonstrates a regulatory role for Corticotropin Releasing Factor Receptor 2 (CRFR2) in angiogenesis. Transgenic mice lacking functional CRFR2 display hypervascularization (Example 16), characterized by increased blood vessel size and number in all examined tissues including the

brain, heart, pituitary gland, and gastrointestinal tract (Example 18, Figures 9 and 10). The increased vascularization is shown to be independent of angiogenesis during embryonic development (Example 17, Figure 8). CRFR2 also affects vascular endothelial growth factor expression, as shown in Example 19 and Figure 12. Increased vascular endothelial growth factor expression was observed in all tissues examined from CRFR2 mutant mice, indicating that CRFR2 has a negative regulatory effect on vascular endothelial growth factor production.

The present invention also indicates that CRFR2, which has been localized to the vascular endothelium, is responsible for the vasodilation caused by subcutaneous injection of urocortin (Examples 10 and 15). Blood pressure was measured in CRFR2 mutant and control mice injected with urocortin; while the control mice displayed a significant drop in blood pressure, the CRFR2 mutant mice showed no significant response to urocortin (Figure 6).

In view of the data showing hypervascularization in the absence of corticotropin releasing factor (CRF) signaling in CRFR2 null mutant mice, one of ordinary skill in the art would reasonably conclude that CRF signaling mediated by well-known CRFR2 agonists such as urocortin and CRF could be used to inhibit angiogenesis.

This reasoning is further supported by the finding that CRF signaling has a negative regulatory effect on vascular endothelial growth factor expression (Example 19 and Figure 12). As discussed above in the prior art of Griffioen, vascular endothelial growth factor is known to be an angiogenesis-promoting factors and one method to interfere with angiogenesis is to inhibit the action of vascular endothelial growth factor (Griffioen, page 249, first column, first full paragraph). Thus, the present invention claims a method of inhibiting angiogenesis in a target tissue comprising the step of administering a well-known CRFR2 agonist such as urocortin or CRF.

Villalona-Calero et al. (1998) demonstrate the state of skill and knowledge in the art and provide an example of using the CRFR2 agonist corticotropin-releasing factor (CRF) to treat an inflammatory condition. Villalona-Calero describes the results of a phase I clinical trial of human corticotropin-releasing factor (hCRF) in patients with peritumoral brain edema. Treatment of rats with subcutaneous administration of hCRF had shown promising results in reducing peritumoral brain edema and prolonging survival (Villalona-Calero et al., page 72, left column, first paragraph). The effects observed appeared to be due to a direct action of CRF on the microvasculature surrounding the tumors (Villalona-Calero et al.,

page 76, Discussion, first paragraph). CRF is identical between rats and humans (Villalona-Calero et al., page 71, Introduction, second paragraph). In human patients, hCRF was found to be well tolerated at doses up to 2 ug/kg/h by continuous infusion over a 72-hour period (Villalona-Calero et al., abstract). Improvement in edema-related symptoms were seen in 10 of 17 patients (page 76, Discussion, second paragraph); whereas 8 patients (including one placebo-treated patient) showed detectable reductions in peritumoral edema (Villalona-Calero et al., Figure 3).

The teaching of Villalona-Calero et al. demonstrates that protocol for the administration of a CRFR2 agonist such as corticotropin-releasing factor is readily available in the art. If the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. Section 112 is satisfied (M.P.E.P §2164.01(c)). Accordingly, Applicants submit that one of ordinary skill in the art could administer a CRFR2 agonist according to the method of Villalona-Calero et al. and practice the claimed method of the instant invention without undue experimentation. Villalona-Calero et al. also teach that CRF have direct action on the microvasculature surrounding the tumors. This is consistent with the finding disclosed herein that demonstrates a role for CRF in

angiogenesis. Thus, taking the prior art and the present disclosure together, one of ordinary skill in the art would predict with a reasonable expectation of success when using a CRF agonist to inhibit angiogenesis. If CRF administration can inhibit peritumoral edema through a direct effect on the microvasculature, then it can predictably inhibit angiogenesis associated with tumor growth or inflammation through a similar direct effect on the microvasculature surrounding the target tissues.

In conclusion, Applicants submit that a person having ordinary skill in this art would be fully enabled to practice the instant invention in view of the high level of skill and knowledge in the art. The knowledge of the art presented above indicates a relationship between angiogenesis and both tumor growth and chronic inflammation, and suggests that anti-angiogenic therapies to treat tumor growth may also apply to the treatment of chronic inflammatory conditions. The increased expression of vascular endothelial growth factor is also linked to conditions involving angiogenesis in both tumor growth and inflammation. Furthermore, the art demonstrates promising clinical results using the CRFR2 agonist CRF as a treatment for symptoms related to peritumoral inflammation, where the observed effects indicated a direct effect of

CRF on the microvasculature. Consequently, the predictability of the art is that one skilled in the art could combine this knowledge with the experimental results in the present application to extrapolate the predicted results of the claimed method. The present application demonstrates that the lack of CRFR2 function leads to increased angiogenesis; that CRFR2 is likely to have a negative regulatory effect on vascular endothelial growth factor expression; and that a CRFR2 agonist can have a direct effect on CRFR2 action in vascular endothelium. Given the known similarity in the role of angiogenesis in the development of both chronic inflammation and tumor growth, one skilled in the art could reasonably expect that increasing the action of CRFR2 by treatment with a known receptor agonist would inhibit angiogenesis. One skilled in the art could also readily adapt the dosage data for CRF treatment provided by the art to determine the dosage regimen of CRFR2 agonist in the practice of the claimed method. Therefore, one skilled in the art would not be required to engage in an amount of experimentation that is above that routinely practiced in the art in order to practice the claimed invention.

For the reasons given above, Applicants respectfully request that the rejections of the Examiner should be reversed, and that claims 20-23 be allowed.

Respectfully submitted,

Date: July 22, 2003

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CLAIMS ON APPEAL

20. A method of inhibiting angiogenesis in a target tissue comprising the step of administering a Corticotropin Releasing Factor Receptor 2 (CRFR2) agonist to said target tissue, wherein said CRFR2 agonist inhibits angiogenesis in said tissue.

21. The method of claim 20 wherein said CRFR2 agonist is selected from the group consisting of urocortin and corticotropin releasing factor.

22. The method of claim 20, wherein said tissue is selected from the group consisting of heart, brain, pituitary, gonad, kidney, adipose, and gastrointestinal tract tissues.

23. The method of claim 20 wherein said angiogenesis is inhibited in an individual having a pathophysiological condition selected from the group consisting of cancer and diabetic retinopathy.